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Attentional updating and monitoring and affective shifting are impacted independently by aging in macaque monkeys

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Abstract

One hallmark of the normal cognitive aging process involves alterations in executive function. Executive function can be divided into at least three separable components, including set shifting, attentional updating and monitoring, and inhibition of prepotent responses. The ability to study the neural basis of cognitive aging has been enriched by the use of animal models such as the macaque monkey. In aged macaques, changes in attentional updating and monitoring systems are poorly understood compared to changes in shifting and inhibition. A partial explanation for this is the fact that the tasks designed to study executive function in aged monkeys, to date, primarily have probed shifting and inhibition processes. Here we examine how aging impacts attentional updating and monitoring processes in monkeys using an interference task designed after a paradigm used to examine multi-tasking in older humans. Young and aged macaque monkeys were tested on this interference task as well as on an object reversal learning task to study these processes in the same animals. Relative to the young monkeys, aged animals were impaired on both tasks. Proactive and retroactive interference did not differ between age groups on an array of 40 object pairs presented each day in the object reversal learning task. The levels of performance on the interference task were not correlated with levels of performance in the object reversal task. These results suggest that attentional updating and monitoring and affective shifting are separable functions in the macaque, and that normal aging affects these mental operations independently.

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Keywords

executive function; interference; cognitive aging; nonhuman primate

1. Introduction

Goal-directed behaviors allow individuals to deliberately select actions that accomplish specific objectives, differentiating them from habitual behaviors, which are executed regardless of context. The mental processes that guide the proper execution of goal-directed behaviors, collectively referred to as executive function, are thought to be supported by neural networks within the mammalian prefrontal cortex (Bizon et al., 2012; Clapp et al., 2011; D'Esposito et al., 1995). Declines in executive function can be detected in early adulthood, and are among the first cognitive impairments to emerge in normative, healthy aging (Moore et al., 2006, 2003; Park et al., 2002; Park and Reuter-Lorenz, 2009; Rapp and Amaral, 1989). Recent extensions in average lifespans worldwide have led to increases in the number of aged individuals (Leeson and Leeson, 2014), highlighting the importance of understanding the neurobiological changes that underlie age-related declines in executive function.

A number of theories have been proposed to account for the diversity of mental operations considered to be involved in executive function (Miyake et al., 2000; Friedman et al., 2006; Chatham et al., 2011). For example, Miyake et al. (2000) suggest that executive processes can be divided into at least three separable functions, including attentional updating and monitoring, set shifting, and inhibition of prepotent responses (Fisk and Sharp, 2004; Miyake et al., 2000). Lesion and functional imaging studies clearly show that different regions of the prefrontal cortex operate independently to give rise to each of these executive functions (Dias et al., 1996; Godefroy et al., 1999; Robbins et al., 1996). For example, in non-human primates, lesions to the orbitofrontal cortex result in performance deficits on an object reversal learning task but not an extra-dimensional set-shifting task, and lesions to the dorsolateral prefrontal cortex result in the exact opposite pattern of impairment (Dias et al., 1996). In the context of normative aging, there is evidence that distinct executive processes change at different rates within and between people (Fernandes et al., 2004; Glisky et al., 2001, 1995), suggesting that distinct prefrontal networks experience age-related neurobiological alterations independently.

Animal models of cognitive aging have enriched our understanding of the brain alterations that underlie lifespan changes in cognition (for reviews see (Bizon et al., 2012; Erickson and Barnes, 2003; Hara et al., 2012; Samson and Barnes, 2013). The macaque monkey provides a particularly valuable model for examining the neural basis of cognitive decline during normal aging since: 1) macaques experience age-related cognitive decline similar to that of humans (e.g., Erickson and Barnes, 2003; Gallagher and Rapp, 1997; Hara et al., 2012; Rapp and Amaral, 1989; Samson and Barnes, 2013), 2) comparative studies of the cytoarchitectonic organization of dorsolateral and ventromedial prefrontal cortical regions in macaques and humans suggest that the two species possess numerous homologous frontal cortical fields, with discrepancies existing only in the size and delineation of these areas

(e.g., Petrides et al., 2012; Petrides and Pandya, 1999), and 3) macaques do not develop dementing neurodegenerative diseases, allowing for studies of normal aging to be carried out at molecular, anatomical and electrophysiological levels of analysis (e.g., Hara et al., 2012; Morrison and Baxter, 2012; Peters et al., 1996).

When cognitive tests similar to those used in humans are administered to monkeys, like humans, older macaques show clear individual differences, with some monkeys showing minimal impairment, some showing severe impairment, and most falling between the two ends of this continuum (e.g., Moore et al., 2006, 2003; Peters et al., 1996; Rapp and Amaral, 1991). Interestingly, tasks designed to assess disparate mental skills within the same group of aged monkeys suggest that distinct aspects of cognition can be impaired differently within an individual monkey (Voytko, 1999). For example, older animals that are impaired on an object-based task may not be impaired on spatial versions of the same task, and *vice versa* (Voytko, 1999). Similarly, Bizon and colleagues have shown that aged rats with impairments on a spatial working memory task can perform normally on a set-shifting task, and rats impaired on a set shifting task can perform spatial working memory tasks without impairment (Beas et al., 2013). Together, these results suggest that normative aging alters different cognitive systems independently of one another within an individual, and the pattern in which different cognitive systems change with age varies between individuals.

Whether different components of the executive function network age independently in non-human primates is not known, and studying this question requires the same individual aged monkeys to perform multiple executive tasks. To this end, the experiments reported here examine the performance of young and aged macaques on two separate tasks that probe the executive processes of attentional updating and monitoring and affective shifting. The first task is an interference task adapted from a multitasking paradigm in humans used to probe attentional updating and monitoring (Clapp et al., 2011; Clapp and Gazzaley, 2012). This task is designed to deliver different forms of interference in the delay period of a delayed nonmatching-to-sample task, requiring animals to switch attention from the primary object recognition task to a secondary task and back. Basile and Hampton (2013) used this paradigm with a matching rule instead of a nonmatching rule to show that interference significantly reduces performance when an active encoding strategy is used. In humans, similar tasks have been shown to engage the lateral and medial frontal cortices, but not ventromedial prefrontal areas (Clapp et al., 2011, 2009; Clapp and Gazzaley, 2012). The second task used in this study is an object reversal learning task, which tests the ability of an animal to alter behavior following changes in the emotional significance of stimuli, a process referred to as affective shifting. Lesion and imaging studies have shown that orbitofrontal cortical, striatal and amygdalar networks underlie affective shifting (Dias et al., 1996; Fellows and Farah, 2003; Iversen and Mishkin, 1970; Rogers et al., 2000; Wheeler and Fellows, 2008; Izquierdo et al., 2016). The execution of both the attentional updating and monitoring and affective shifting tasks in the same set of monkeys allow us to evaluate whether these separate executive processes are affected independently by the aging process or whether there is a common age-related pattern of decline across individual monkeys and executive processes.

2. Materials and methods

2.1. Subjects

Six young (mean: 10.5 years) and seven aged (mean: 23.4 years) female bonnet macaques (*Macaca radiata*) participated in the current study. Every monkey received a semiannual health assessment from the veterinary staff at the University of Arizona (Tucson, AZ), and no animal included in this study presented with health concerns before or during the time of testing. Animals were paired-housed in a humidity- and temperature-controlled vivarium with a 12 hours light-dark cycle and ad libitum food and water. Prior to testing, all animals underwent behavioral shaping to tolerate restraint in a specialized non-human primate transport box (50.8 cm × 31.1 cm × 40 cm), which was used to transport the monkeys from their home vivarium to the behavioral testing box (below). The experiments described followed guidelines established by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee at the University of Arizona.

2.2. Testing apparatus and task stimuli

A modified Wisconsin General Testing Apparatus (WGTA; Harlow and Bromer, 1938) was used to acquire all behavioral data (based on Baxter et al., 2000). The WGTA consists of a box where animals reside during the testing procedure. At one end of the box vertical bars separate the animal from a tray with three equally spaced wells where stimulus presentation and reward delivery occur. Two partitions could be manipulated by the experimenter to control the animal's access to and visibility of the stimulus objects and rewards. The first partition consisted of a wooden guillotine door, and served to block the monkeys from both visualizing and interacting with the objects/rewards. A transparent Plexiglas door was used as the second partition, which allowed the animals to visualize the objects/rewards, but not to interact with them. A one way mirror separated the experimenter from the animals, allowing their performance to be monitored without detection. Stimuli consisted of plastic toy objects of comparable size (~ 8cm³), and the rewards used were dry and fresh fruit, vegetables, and sugar free gummy bears.

2.3 Behavioral Paradigms

2.3.1 Delayed nonmatching-to-sample task with differing levels of interference

—The delayed nonmatching-to sample (DNMS) task (Rapp and Amaral, 1991) begins with a single object presented over the center well of the WGTA (Figure 1A) – this is the “sample phase”. Animals are allowed to displace the object to receive a food reward, ensuring that the sample object is encoded. Following the sample period, the wooden guillotine door is closed for a delay period of 30 seconds. After the delay period, the sample object is presented alongside a novel object on each of the lateral wells (this is the “test phase”). Only the novel object is baited, and the monkey must learn this rule through trial and error. Objects were presented in a trial-unique manner, ensuring that monkeys only encountered each object once over the course of the experiment to avoid any biases that may arise from repeated object presentation. Each animal performed 20 trials daily until reaching a 90% performance criterion over 5 consecutive days. Once criterion performance on the DNMS task had been achieved, the monkeys were trained on an object discrimination task with 4 pairs of objects (Figure 1B). In the object discrimination task the animals are presented two

objects on each of the lateral wells, one baited and one not baited, and through trial and error the monkey must learn the object-reward association of each pair. To maintain a high level of performance on the DNMS task during object discrimination training, monkeys performed 20 discriminations daily with the 4 pairs of objects (presented 5 times for each pair) and 10 trials of the DNMS task each day, alternating which task came first. Criterion performance was reached when the monkey achieved 90% performance for both tasks over 5 days.

After reaching criterion, three forms of interference (described below) were presented during the 30 sec delay period of the DNMS: 1) an interruption condition (Figure 1B) in which the monkeys were required to complete an object discrimination problem during the delay interval, forcing animals to shift attention to a secondary task prior to making the final choice in DNMS, 2) a relevant distraction (Figure 1C) condition that required animals to displace a single object for food reward during the delay period prior to completing the DNMS, and 3) an irrelevant distraction (Figure 1D) condition in which a transparent Plexiglas barrier was lowered and the monkey could view a single object behind this barrier, but could not interact with it nor did it receive a food reward. The relevant distraction condition served as a motor and food reward control for the interruption condition, as both conditions require a motor response and deliver food reward. Unlike the interruption condition, however, the relevant distraction condition does not require attention to object features for a correct response. The irrelevant distraction condition in which animals could view the distracting object, but were prevented from interacting with it or receiving a food reward, tested the animal's ability to ignore task irrelevant stimuli. The stimuli for the interruption, distraction and irrelevant distraction conditions were all presented 10 seconds after the presentation of the DNMS sample object. These three stimuli were kept in front of the animal for 10 seconds before being removed, and the DNMS test phase came 10 seconds after the interference stimuli were removed. Thus, the total delay period of the DNMS with interference task was 30 seconds in all conditions. Figure 1A through D present pictorial depictions of the DNMS interference paradigm.

2.3.2 Object reversal task—The training protocols and description of the object reversal learning task are described in detail elsewhere (Burke et al., 2014). Briefly, in the first phase of the object reversal task, monkeys learned 40 two object discrimination problems. Each day the animals were presented with 40 object pairs that each began as novel and were presented in the same order. Through trial and error the monkeys determined which object in the pair would always be associated with a food reward. At the beginning of each trial, the objects were hidden from the animals by a wooden partition. Once the guillotine door was lifted the animals were required to displace a single object and receive the food reward if they selected the correct object. The rewarded and unrewarded objects did not change for the duration of the object discrimination learning period, and monkeys performed this task daily until they reached a 90% performance criterion over 5 consecutive days (180/200 trials). After reaching criterion, the reversal learning component of the task was presented. During this phase of the task, the rewarded and unrewarded objects in each pair were switched, and the animals were required to learn this novel association rule. Again, the monkeys performed this reversal task until reaching the same 90% criterion over 5 consecutive days after which

testing on the object reversal task was complete. Figure 1E presents a schematic depiction of the object reversal paradigm.

2.4. Data analysis

2.4.1. DNMS task with differing levels of interference—For each animal, 4 different conditions were administered within the delay portion of the DNMS task: 1) no interference (delay alone, standard condition; Figure 1A); 2) interruption within the delay (performing a simple object discrimination task, one object rewarded, Figure 1B); 3) relevant distraction (retrieving reward from a single object, this object always rewarded, Figure 1C); and 4) irrelevant distraction (viewing a single object behind a transparent partition, no reward, Figure 1D). For each animal, the proportion of correct responses and reaction time in the four separate conditions were used as performance metrics. To test for the specific effect of age on the different tasks, a linear mixed-effects model (LMM) was fit to the data. The proportion of correct responses, $Y_{i,t}$, for animal i and task t was modeled using

$$Y_{i,t} = b_0 + b_1 \text{Age}_i + b_2 \text{Task}_t + b_3 \text{Age}_i * \text{Task}_t + r_i \quad (1)$$

where Age_i was a binary categorical variable corresponding to young and old age groups and Task_t was a categorical variable corresponding to use of no distraction, irrelevant distraction, relevant distraction and interruption conditions, respectively. A random effects intercept term, $r_i \sim N(0, \sigma_{r_i}^2)$, was included to account for inter-animal variability. The model was fit using a maximum likelihood approach in MATLAB (MATLAB and Statistics Toolbox Release 9.0.0.341360, R2016a; the MathWorks, Inc., Natick, MA). To check appropriateness of the model, a post-fitting assessment was made such that a plot of the residuals versus fitted values showed no trend. To assess the necessity of adding the random effects intercept term, we also fit a model with no random effects term. Comparison of the two models using the theoretical likelihood ratio test indicated that inclusion of random effects was necessary ($p < 2.1 \times 10^{-9}$). In the text, this model's statistics are reported in terms of, t -statistic, degrees of freedom and a p -value. The same approach was used for the reaction time data (on a slightly reduced data set as there was no reaction time data for two of the monkeys). Reaction time was defined as the time from object presentation to the time that the animal touched the chosen object, and was measured using infrared beams that detected the monkeys reach from the holding box to interact with the objects.

2.4.2. Object reversal—For the object reversal task (Figures 4–6), the temporal progression of learning of each object was tracked for each animal as a function of day, generating 40 learning curves per animal. A state-space modeling approach was used to compute the learning curves using Bernoulli observation models (Smith et al., 2004). For each animal a learning curve, its 90% confidence bounds and a learning trial was estimated for acquisition of the object discrimination task and its reversal. The learning day was defined as the day for which the learning curve (its lower confidence boundary) exceeded and remained above chance for the remainder of the experiment (Figure 4). It is this learning day that is compared across age groups (Figures 5–6). Learning curve model estimation was performed using a Bayesian approach (Smith et al., 2007) in Python using the Monte Carlo

package, pymc3, assuming the initial condition is unknown and applying an exponentially-distributed prior for the variance of the underlying state with parameter, $\lambda = 50$. The results were estimated based on 2000 Monte Carlo samples after a 1000 sample burn-in period.

Once learning day was computed, between-group comparisons were made using two linear mixed models. The first model for learning day, L_j , is identical to the model in Eq (1). In the second model, the 40 objects shown per day were grouped into three time epochs based on their order of presentation. Specifically, the first fourteen objects were in the first epoch, the middle twelve were in the second epoch, and the final fourteen were in the third epoch. The average learning trials of each object within these three epochs were then compared on an individual animal basis (i.e. the learning day $L_{i,t,j}$ for animal, i , on task, t , for epoch, j , was modeled by the linear mixed model)

$$L_{i,t,j} = b_0 + b_1 I(\text{Task}_{i,2,j}) + b_2 I(\text{Epoch}_{i,t,2}) + b_3 I(\text{Epoch}_{i,t,3}) + b_4 I(\text{Task}_{i,2,j}) * I(\text{Epoch}_{i,t,2}) + b_5 I(\text{Task}_{i,2,j}) * I(\text{Epoch}_{i,t,3}) + r_i$$

(2)

where $r_i \sim N(0, \sigma_b^2)$ is a random effects term that accounts for inter-animal variation and b_i ($i=0, \dots, 5$) are constants estimated by maximum likelihood. The indicator variable $I(\text{Task}_{i,2,j})$ is a dummy variable taking the value zero when the OD task is applied and one when the RL is applied. The dummy indicator variables $I(\text{Epoch}_{i,t,2})$ and $I(\text{Epoch}_{i,t,3})$ are zero except during epochs 2 and 3 when they take the value one, respectively.

2.4.3. Relative impairment scores—For the DNMS task, the extent of impairment for a given animal is approximated by the percentage correct in the test phase of the DNMS with interruption, divided by the percentage correct in the test phase of the DNMS task alone (no interference). For the reversal task, impairment is measured by subtracting the number of days required for original acquisition of the object discrimination from the number of days required to learn the reversal component of the task (i.e., reversal learning day – object discrimination day for each animal).

3. Results

3.1 Results for DNMS task with differing levels of interference

3.1.1 Performance of the DNMS task—Young and aged monkeys were trained on the DNMS task to a performance criterion of 90% over 5 consecutive days. Aged monkeys required more trials to reach this performance criterion than did young monkeys, although this difference did not reach statistical significance (aged mean: 1300 trials; aged standard deviation: 590 trials; young mean: 812 trials; young standard deviation: 13 trials; ANOVA $p = 0.13$). This pre-training ensured that young and aged monkeys exhibited the same levels of performance on the DNMS alone condition (LMM, main effect of age, t -stat = 0.70, $df = 44$,

$p = 0.49$; Figure 2). Thus, any age differences in performance of the DNMS task during the interference conditions could be attributable to effects of those intervening tasks rather than to performance differences on the DNMS task itself.

3.1.2 Irrelevant distraction condition impaired DNMS performance in young and aged monkeys—Performance on the DNMS task in the irrelevant distraction condition was worse than performance on the DNMS task with no interference (LMM, DNMS-ID, t -stat = 2.6, $DF = 44$, $p = 0.014$) in both age groups (LMM, AGE*DNMS-ID interaction, t -stat = -0.46 , $DF = 44$, $p = 0.640$; Figure 3A). For both age groups, reaction times were faster in the DNMS alone condition than in the DNMS with irrelevant distraction condition (LMM, DNMS-ID reaction time, $p = 0.0001$; Figure 3B).

3.1.3 Relevant distraction condition did not impair DNMS performance in young and aged monkeys—Performance on the DNMS task in the relevant distraction condition was not different from performance on the DNMS task with no interference (LMM, DNMS-AD, t -stat = 1.3, $DF = 44$, $p = 0.21$), and was not affected by age (LMM, AGE*DNMS-AD interaction, t -stat = -1.7 , $DF = 44$, $p = 0.10$; Figure 3C). Reaction times in the DNMS with relevant distraction condition were not different from those in the DNMS condition with no interference (LMM, DNMS_AD, t -stat = -1.5 , $df = 36$, $p = 0.15$; Figure 3D) and were not affected by age (LMM, AGE*DNMS-OD interaction, t -stat = 1.3, $DF = 36$, $p = 0.21$).

3.1.4 Interruption condition impaired aged and young monkeys' performance on the DNMS task—Performance on the DNMS task in the interruption condition was worse than performance on the DNMS task with no interference (LMM, DNMS-OD, t -stat = 3.9, $DF = 44$, $p = 0.0004$), and aged monkeys performed worse than did young monkeys (LMM, AGE*DNMS-OD interaction, t -stat = -2.2 , $DF = 44$, $p = 0.032$; Figure 3E). Reaction times in the DNMS with interruption condition were not different from the DNMS condition with no interference (LMM, DNMS_OD, t -stat = 0.043, $df = 36$, $p = 0.96$; Figure 3F) and were not affected by age (LMM, AGE*DNMS-OD interaction, t -stat = 1.3, $DF = 36$, $p = 0.21$).

3.2 Results for object reversal learning task

3.2.1 Aged monkeys are significantly impaired on the object reversal task—Figure 4 shows the performance of representative young and aged monkeys on the object discrimination and reversal learning tasks. Both young and aged animals required more trials to reach the learning criterion during the reversal learning task compared to the object discrimination task (LMM, main effect of task, t -stat = -8.7 , $df = 24$, $p = 7.6e-9$, Figure 5). Older animals required more trials to reach learning criterion on both tasks (LMM, main effect of age, t -stat = -3.7 , $DF = 24$, $p = 0.001$, Figure 5). The degree of this age impairment in the object discrimination and reversal learning tasks were not different (LMM, age*task interaction, t -stat = 0.46, $df = 24$, $p = 0.65$).

3.2.2 Evidence for proactive and retroactive interference on object discrimination and reversal learning—To determine whether objects at the beginning,

middle or end of the association pair list were learned differentially, objects were grouped into three time epochs based on their order of presentation. Specifically, the first fourteen objects were in the first group, the middle twelve were in the second group, and the final fourteen were in the third group. The average learning trials of each object within these three groups were then compared on an individual animal basis. During both tasks, the second and third group of objects were learned significantly faster than were the first objects (LMM, main effects of second (third) epoch, $t_{stat} = -5.4(-3.8)$, $DF=1114$, $p = 9.9e-8$ ($1.3e-4$); Figure 6). Additionally, the middle third of objects were learned significantly faster than the last third of objects (LMM, Coef. Test, $F = 1.6e+01$, $DF = 1108$; $p = 7.1e-5$; Figure 6). There was no difference between age groups in any of these measurements. These results suggest that young and aged monkeys did not show either a 'primacy' or 'recency' effect on learning these associations, but rather experience some level of proactive and retroactive interference during associative and reversal learning (see discussion).

3.3 Performance on the DNMS interruption condition was independent of performance on the object reversal task

To examine whether those monkeys with poor performance on the DNMS interruption condition also were particularly impaired on the object reversal task, we obtained relative impairment scores for every individual animal on both tasks (described in Materials and methods). There was no significant relationship between these performance measures in either young or aged animals (young: $r = -0.22$ $p = 0.67$, aged: $r = -0.16$ $p = 0.73$; Figure 7).

4. Discussion

4.1. Novel findings

The main novel findings of the present study are that 1) aged macaques exhibit greater performance deficits than do young macaques in an object recognition task when interference requiring attentional shifts intervene; 2) both young and aged monkeys exhibit proactive and retroactive interference during an affective shifting task; and 3) deficits in attentional updating and monitoring were independent of deficits in affective shifting. Together these results indicate that aging impacts distinct components of executive function independently.

4.2 Interruptions during the delay of a DNMS task negatively impact aged monkeys more than young monkeys

Basile and Hampton (2013) have shown that young monkeys are impaired on a delayed matching-to-sample task with interference only when the choice is actively maintained in memory, but not when a passive maintenance strategy is used. The present study used the nonmatching rule with interference to test the ability of monkeys to disengage from and reengage with a memory representation during conditions akin to multitasking (Figure 1A). Both young and aged monkeys were impaired on the DNMS task when interruptions (Figure 3E) and irrelevant distractions (Figure 3A) were presented during the delay, suggesting that the animals may have used an active maintenance strategy in this task. Aged animals were negatively affected by interruptions more than were young monkeys, but equally affected by

irrelevant distractions. Differences in the attentional requirements in the interruption and irrelevant distraction conditions may explain these effects (discussed below).

Gazzaley and colleagues have shown that different forms of attention are altered uniquely during normative aging. For example, unimodal sensory processing and attention are degraded in aged human subjects, while similar demands presented in a crossmodal context do not elicit age-related impairments (Clapp et al., 2011; Mishra and Gazzaley, 2013). Completion of the DNMS with interruption condition and DNMS with irrelevant distraction condition require different aspects of attentional updating and monitoring to complete. The interruption condition requires animals to shift attention from the DNMS task to the object discrimination task and back. The irrelevant distraction condition does not require a shift in attention, but does require animals to suppress attention towards the task irrelevant stimuli. The current data suggest that, in macaques, attentional shifting is negatively impacted by aging, while attentional suppression is not.

In humans, the neural structures implicated in attention shifting and suppression involve distinct regions of the prefrontal cortex (Clapp et al., 2011; Chadick et al., 2014; Gazzaley and D'esposito, 2007). Clapp et al. (2011) demonstrated that the middle frontal gyrus of the dorsolateral prefrontal cortex functionally connects with different visual cortical regions during attentional shifts between tasks. Conversely, top-down modulation of sensory information appears to arise from the medial prefrontal cortex, anterior cingulate cortex, parietal cortex, and the medial temporal lobe (e.g., Chadick et al., 2014; Colby and Goldberg, 1999; Birrell and Brown, 2000; Behrmann et al., 2004; Buschman and Miller, 2007; Gazzaley and D'esposito, 2007; Rissman et al., 2009).

Functional connectivity analyses in human subjects performing a task similar to the one described here, indicate that aged subjects, compared to young, do not show dynamic switching between functional brain networks in lateral frontal cortex and higher-order visual cortical regions (Clapp et al., 2011). While the brains of older individuals were able to switch to higher order visual networks representing the interruption condition, their brains effectively became stuck there, and failed to switch back in a network state that represented the primary task. This deficit might be explained by the concept of backward inhibition, or the inability to disengage from a recently completed task. In fact, aged humans have been shown to be impaired on tasks requiring this process (Hasher et al., 1999; Hübner et al., 2003; Mayr and Keele, 2000).

4.3 Implications for cohort effects in human studies

Older humans tend to have less exposure to technology than do younger individuals, and it has been proposed that cohort differences in technological abilities contribute to age-related differences in the performance on cognitive tasks (for review see Charness and Boot, 2009). One strength of the current study is the ability to control for generational effects by ensuring that young and old age groups are exposed to similar testing and living conditions over their lifespan. The detrimental effects of interference on object recognition memory in older nonhuman primates argues that multitasking deficits observed in older humans do not simply reflect cohort effects. Rather, the observed multitasking deficits most likely arise

from dysfunction of prefrontal cortical circuits that occurs during normative biological aging (e.g. Clapp et al., 2011; Clapp and Gazzaley, 2012).

4.4. Aged macaques are impaired at affective shifting

Reversal learning paradigms have been used to study executive function in macaques for decades (e.g., Bartus et al., 1979; Divac et al., 1967; Rapp, 1990). The mental process primarily probed in the reversal learning task is affective shifting, which requires unlearning an initial stimulus-reward association and replacing it with a new association when the reinforcement is switched. Performance on this task is thought to reflect the ability to alter behavior based on changes in the emotional valence of stimuli, and has been suggested to provide a measure of cognitive flexibility (Hara et al., 2012). Compared to young monkeys, aged monkeys have been shown to require more trials to reach learning criterion during the reversal learning component of the task, but are unimpaired in learning the initial associations during the object discrimination component of the task (Bartus et al., 1979; Divac et al., 1967; Hara et al., 2012; Rapp, 1990). The current group of aged monkeys performed worse than young monkeys on both the object discrimination and reversal learning components of the tasks (Figure 5), suggesting an impairment in both associative learning and affective shifting. Species differences (bonnet macaque vs rhesus macaque), more sensitive analytic methods used here, or prior exposure to complex tasks in the present animals (e.g. DNMS with interference task) could account for the discrepancy between the current data and previous findings (Bartus et al., 1979; Divac et al., 1967; Hara et al., 2012; Rapp, 1990).

While the full extent of the neural networks underlying object reversal learning are still being elucidated, both imaging and lesion studies performed in humans and nonhuman primates have consistently implicated the orbitofrontal cortex (Walker's areas 11,13, and 14) and the medial prefrontal cortex (e.g., Fellows and Farah, 2003; Iversen and Mishkin, 1970; Rogers et al., 2000; Wheeler and Fellows, 2008). In addition to these cortical regions, the dorsal striatum, ventral striatum and basolateral nucleus of the amygdala have also consistently been implicated as non-cortical brain areas involved in reversal learning (for reviews see Genovesio and Tsujimoto, 2014; Izquierdo et al., 2016). Importantly, it is becoming clear that these individual brain regions do not support reversal learning in isolation. Rather, it is the interaction of this cortical-striatal-amygdalar network that is required. For example, Rudebeck and colleagues demonstrated that fiber-sparing lesions of the orbitofrontal cortex in macaques does not impair object reversal learning (Rudebeck et al., 2013), suggesting that the white matter, but not grey matter in this region is necessary for reversal learning. Whether these white matter tracts connect subcortical regions with the orbitofrontal cortex or are fibers of passage remains to be clarified.

Interestingly, the volume of the orbitofrontal cortex was examined in the same cohort of macaques used in the present study, and the number of perseverative errors on the reversal learning task did not correlate with orbitofrontal cortex grey matter volume (Burke et al., 2014). Orbitofrontal cortex grey matter volume did, however, correlate with performance on a reward devaluation test. This indicates that the orbitofrontal cortex plays a role in updating the value of stimuli, which is a key component of the reversal learning task, but is a separate

cognitive operation from affective shifting. Under this view, the neural networks that underlie affective shifting, perhaps located in non-cortical areas such as the striatum or basolateral nucleus of the amygdala, use the stimulus-associated reward information provided by the orbitofrontal cortex during reversal learning.

4.5. Proactive and retroactive interference during associative and reversal learning

In the object reversal learning paradigm, 40 total object pairs were presented daily in the exact same order, allowing for an analysis of serial position effects on the acquisition and reversal of these associations. For example, there is a well-known bias towards remembering items both at the beginning (primacy effect) and at the end (recency effect) of a list (e.g., Murdock 1962; Glanzer and Cunitz 1966). Somewhat surprisingly, in the present study, we did not observe a primacy or a recency effect in either the acquisition or reversal components of the task. Rather, objects encountered in the middle third of trials on each day were learned faster than were objects encountered in the first and last third of trials. This may suggest over-riding effects of proactive interference (when learned information disrupts the ability to learn subsequently presented information) and retroactive interference (when newly formed associations disrupt the recall of previously encoded information) in these types of associative learning and affective shifting tasks. In the present study, associations formed at the beginning of a session likely experience the greatest amount of retroactive interference since the majority of object pairs follow them. The opposite trend would be expected for the effects of proactive interference on the array of object pairs. These two forms of interference are thought to arise through different neural mechanisms and would be expected to exert their effects independently of one another (e.g., Irlbacher et al., 2014; Nee and Jonides, 2008; Jonides and Nee, 2006; Nee et al., 2007). Interestingly, the effect sizes of the ‘middle-list advantage’ were not different between young and aged monkeys, suggesting that there is a similar susceptibility to proactive and retroactive interference in these animals.

To explain the present data, the effects of proactive and retroactive interference cannot simply be additive – rather, they must exert stronger influence at the beginning and ends of the lists, and this may interact with the number of object-pair associations encountered to produce the middle-list advantage. The finding that old and young monkeys are equally prone to the effects of proactive and retroactive interference in the context of associative learning and its reversal, is in contrast to the age deficit observed on the DNMS task with interruption (Figure 3). This dissociation provides further support for the idea that the networks that underlie the DNMS with interference task are separable from those involved in object reversal learning. This could either imply completely independent circuits, or that redundant cortical systems exist to compensate for age-related brain changes in the latter task but are not recruited in the former.

4.6. Deficits in attention shifting and affective shifting do not correlate

Performance on the DNMS task with interruption did not correlate, within an individual monkey, with performance levels on the object reversal task. While these results require replication, they are consistent with the idea that attentional updating and monitoring and affective shifting are independently affected by normative aging (Fisk and Sharp, 2004; Miyake et al., 2000). From a neurobiological perspective, dissociations such as these suggest

that the pattern of network dysfunction is variable between individuals, and such variability can be noted at molecular, anatomical, electrophysiological and behavioral levels (Gray and Barnes, 2015). Further work will be required to specifically define the circuits underlying different components of executive function. The present results suggest, however, that aged monkeys with affective shifting deficits should have distinct patterns of age-related network alteration compared to animals with attentional updating and monitoring impairments. This is reminiscent of the suggestion made by Glisky and colleagues that a major challenge in cognitive aging research is to identify the unique behavioral and neurobiological profiles of individuals (Fernandes et al., 2004; Glisky et al., 2001, 1995). A better understanding of the unique brain-behavior relationship of each individual resulting in memory loss during normative aging may facilitate the development of more targeted treatment approaches for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

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Highlights

- Macaques show age impairments on both shifting and attentional control.
- Monkeys show evidence of retroactive and proactive interference.
- Age-related deficits in attentional monitoring and shifting were independent.

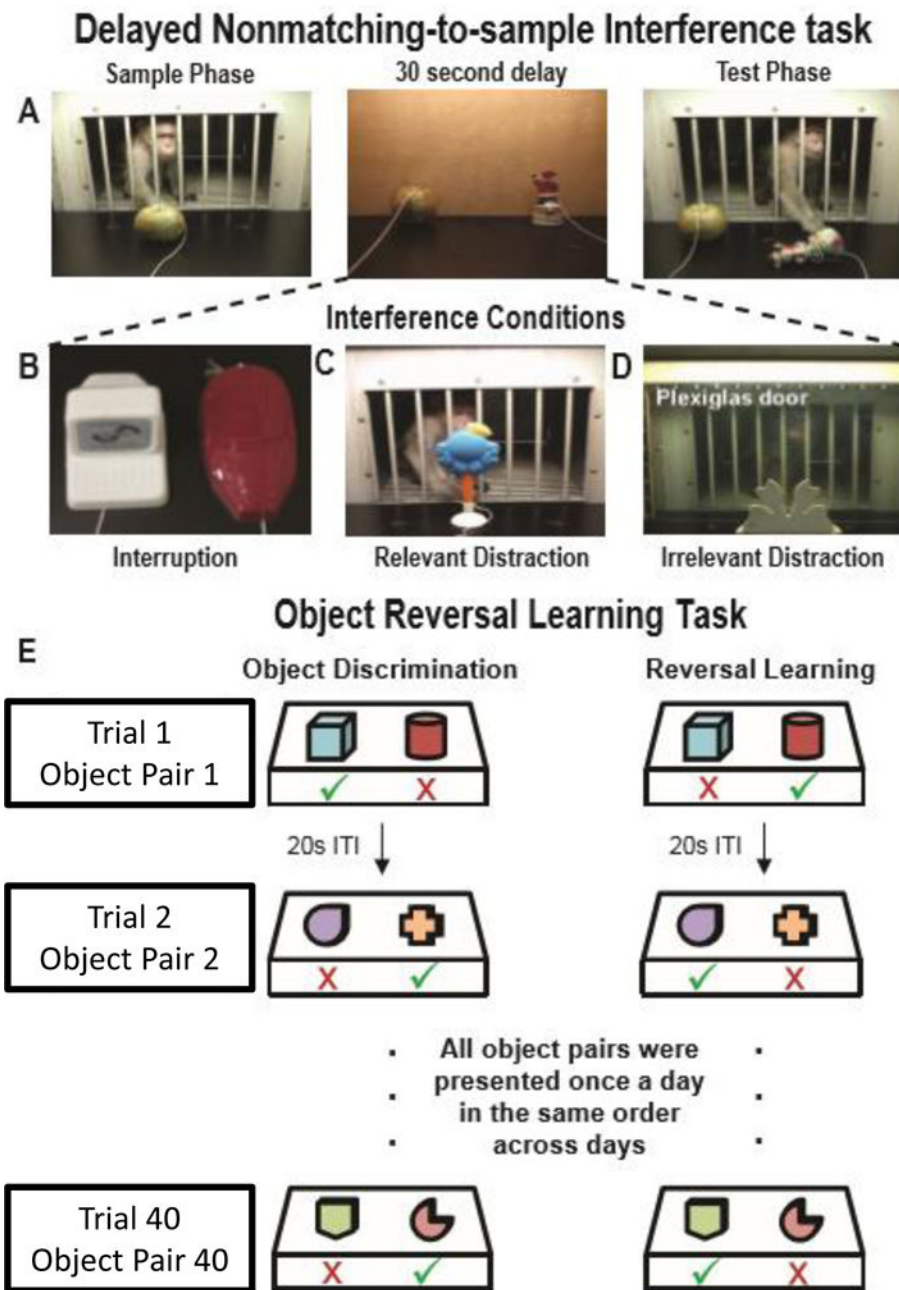


Figure 1. Depictions of the delayed nonmatching-to-sample (DNMS) interference paradigm and the object reversal learning paradigm. **A)** Monkeys learned a DNMS task in a Wisconsin General Testing Apparatus (WGTA) using trial-unique objects, ensuring that the monkeys do not develop a bias towards any particular object. In the sample phase of the task, a single object is presented over the middle of three wells. A 30 second delay period follows the sample phase. During this delay a wooden guillotine door separates the animal from the wells in the testing apparatus. The test phase follows the delay. In this phase two objects, the sample object and a novel object, are presented over the lateral two wells of the apparatus.

Only the novel object is baited, and the monkey must displace this object to receive food reward. After animals reach a 90% performance criterion over 5 days, three interference test conditions are implemented during the delay period of the DNMS task. **B)** An '**Interruption Condition**' in which the monkey had to perform an object discrimination task during the delay, **C)** a '**Relevant Distraction Condition**' in which an object could be moved to obtain a reward, and **D)** an '**Irrelevant Distraction Condition**' in which an object was presented but could not be touched. **E)** The object reversal learning task required monkeys to learn 40 novel object pairs presented sequentially in the same order every session until they reached a 90% performance criterion (**Object Discrimination**). After reaching criterion, the object-reward associations were switched (**Reversal Learning**), and the monkeys re-learned the new associations to the same 90% criterion.

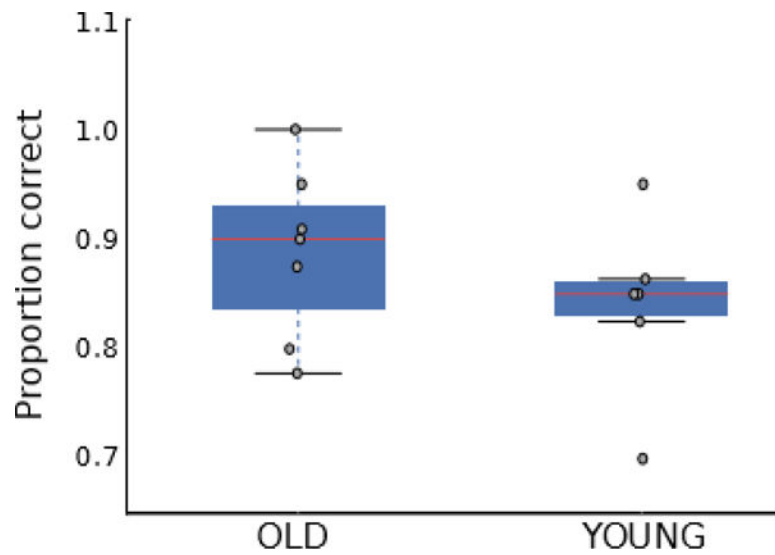


Figure 2. Performance on the DNMS alone condition in young and old monkeys. Boxes indicate the interquartile range (IQR) with whiskers extending to the most extreme data points that are no more than $1.5 \times$ IQR from the edge of the box. Red line indicates median values. Grey circles are jittered so that individual animal performance scores can be more easily seen. There is no difference between age groups after reaching asymptotic behavioral levels.

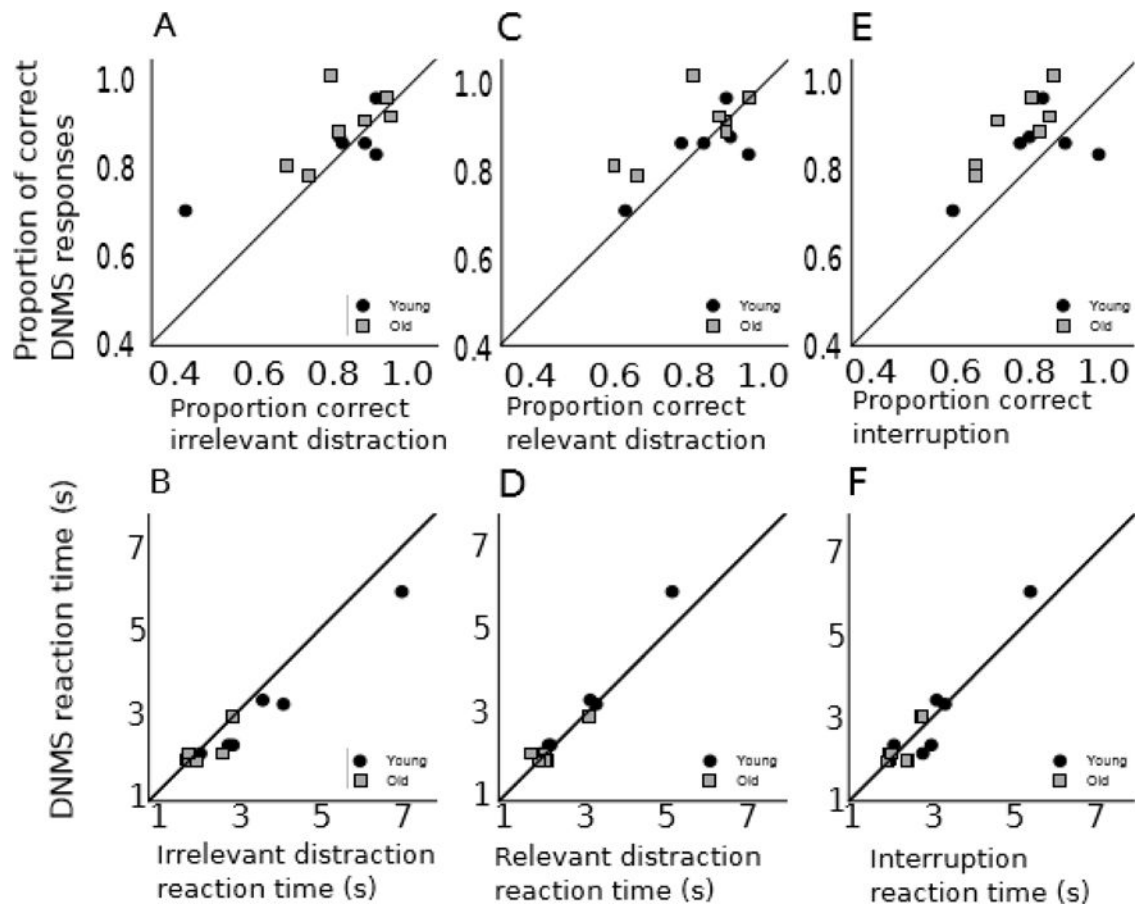


Figure 3.

Effects of irrelevant distraction, relevant distraction and interruption conditions on accuracy of choice performance on the DNMS task (Panels **A**, **C**, and **E**) and on reaction time (Panels **B**, **D** and **F**) for all animals. In all plots black circles represent individual young monkeys and light grey squares represent individual aged monkeys. All diagonal lines represent the unity line, where performance or reaction times from both conditions are equal. Note that performance and reaction time after the relevant distraction condition does not significantly deviate from the unity line in either age group (**C**, **D**). For the irrelevant and interruption conditions, performance of both young and old animals significantly deviated from the unity line (poorer performance; **A**, **E**). Reaction times in the irrelevant distraction condition were slower than in the DNMS alone condition (**B**), whereas reaction times in the interruption condition did not differ from the DNMS alone (**F**).

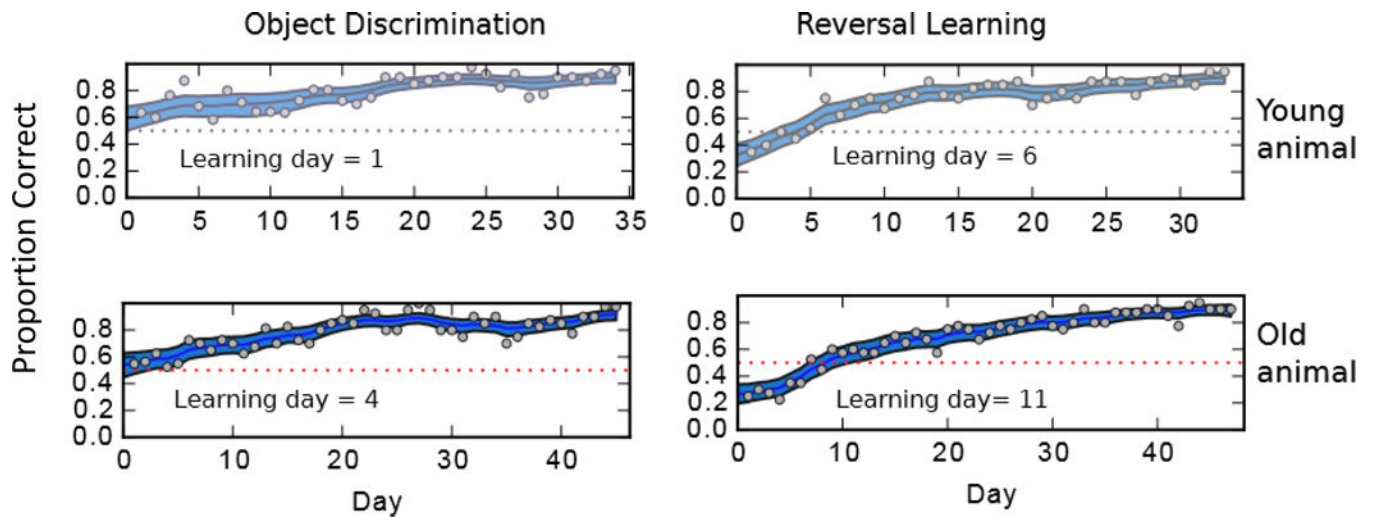


Figure 4. Example performance for one young (top row) and one aged (bottom row) monkey for the object discrimination task (left column) and reversal learning task (right column). Raw proportion of correct responses per day are shown as grey circles. Blue shaded area indicates the 90% confidence bounds for the learning curves as estimated by a state-space model. The probability of a correct response by chance is indicated by the horizontal red dashed line at 0.5. The estimated learning day (the day that performance is estimated to be more than 95% greater than chance) is indicated by numbers inside in each figure.

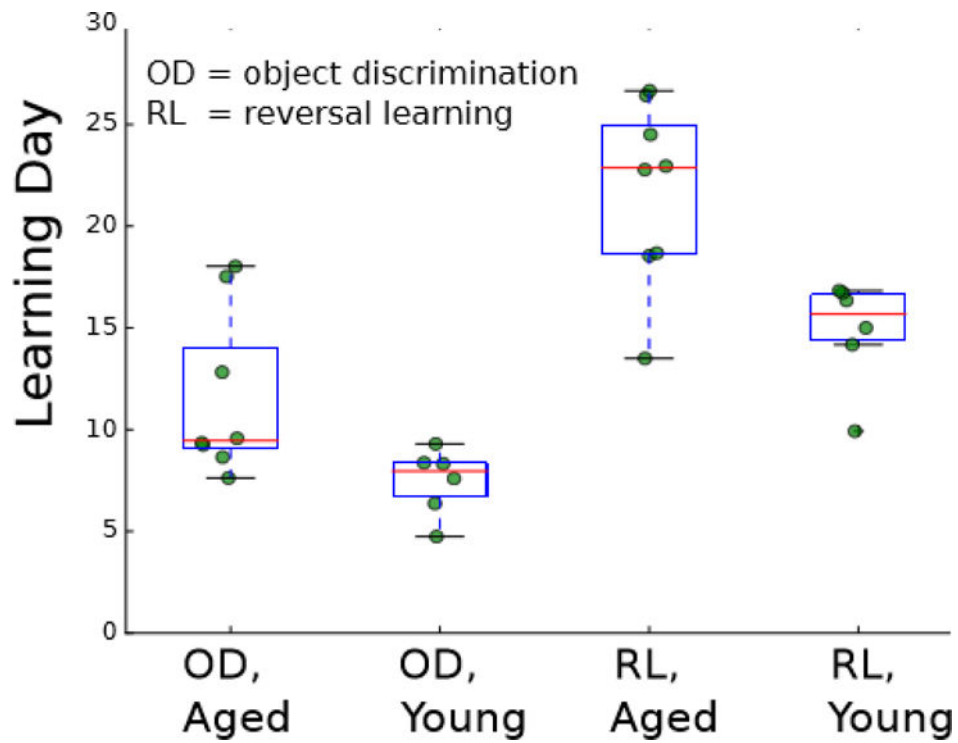


Figure 5.

Estimated learning days for young and aged animals for the object discrimination and reversal learning tasks. Green circles are jittered so that individual animal performance scores can be more easily seen... Boxes indicate the interquartile range (IQR) and whiskers are extended to the most extreme data points that are no more than $1.5 \times$ IQR from the edge of the box. Red line indicates median values. Both young and aged monkeys required more trials to reach the learning criterion in the reversal learning component of the task compared to the object discrimination component. Aged animals required more trials to reach learning criterion in both components of the task.

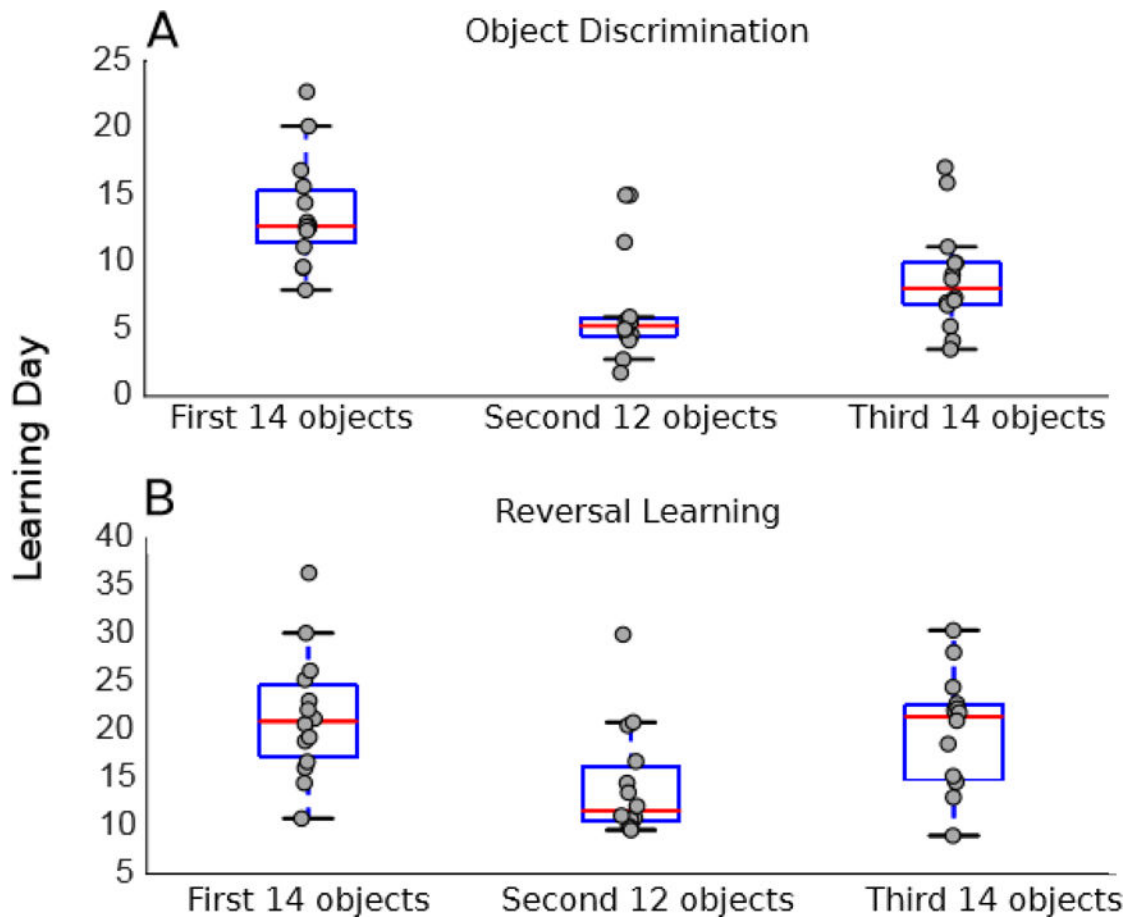


Figure 6.

Comparison of learning days for old and young monkeys combined for the first 14 objects, the second 12 objects and the final 14 objects of the object pair array (40 pairs total). **A**) object discrimination and **B**) reversal learning tasks. Box and whiskers indicate the interquartile range (IQR) and the most extreme data points that are no more than $1.5 \times$ IQR from the edge of the box, respectively. Red line indicates median values. Grey circles are jittered so that individual animal performance scores can be more easily seen. Note that in both cases, the middle third of objects were acquired faster than objects at the beginning or end of the list.

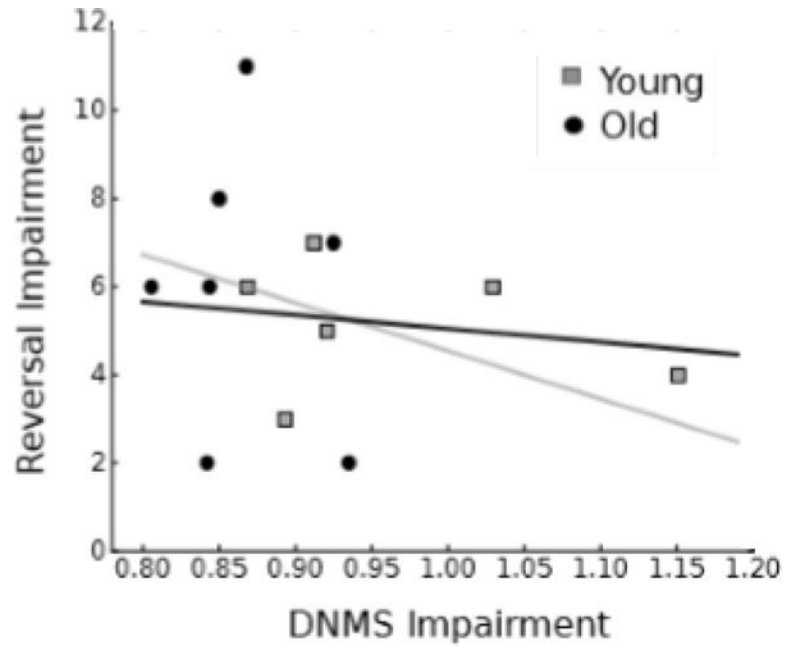


Figure 7.

Performance on the reversal learning task compared with performance on the DNMS with interruption task. Relative impairment scores for the object reversal learning task were obtained by subtracting the learning day on the object discrimination task from the learning day on the reversal learning task (y-axis). Relative impairment scores for the DNMS with interruption task were obtained by dividing the performance on the DNMS with interruption condition by performances on the DNMS alone condition (x-axis). Young and old animals' data are indicated with grey squares and black circles, respectively. Trend lines for the young and old data are in grey and black, respectively. Note that there is no relationship between the impairment scores on these two tasks.